MASTER'S THESIS

Body composition and physical function during chemotherapy for metastatic breast cancer - a pilot observation study

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BODY COMPOSITION AND **P**HYSICAL FUNCTION DURING CHEMOTHERAPY FOR METASTATIC BREAST CANCER – A PILOT OBSERVATION STUDY

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Glossary

BMI	Body Mass Index; weight (kg), divided by height (metres) squared
BC	Breast Cancer
CT	Computed Tomography
COPD	Chronic Obstructive Pulmonary Disorder
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EWGSOP	European Working Group for Sarcopenia in Older People
FFM	Fat Free Mass
FFMI	Fat Free Mass Index
FM	Fat Mass
FMI	Fat Mass Index
MST	Malnutrition Screening Tool
mTOR	Mechanic Target of Rapamycin (signalling pathway)
PF	Physical Function
PG-SGA	Patient Guided Subjective Goal Assessment
QOL	Quality of Life
RCT	Randomised Control Trial
R.V.	Reference Values

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PART 1.0 Introduction

Breast cancer (BC) is one of the most studied malignancies in the world [1], and for good reason; it affects 1 in every 8 women in Australia, is the most common form of cancer amongst women [2], and is considered one of Australia's largest health burdens [3]. In Australia, early-stage BC 5-year survival rates are approximately 90%; however, 1 in 20 women whose disease is confined to the breast, and 1 in 6 women whose BC has reached adjacent tissue, will eventually progress to metastatic disease [4]. Five-year survival rates of advanced disease drop to only 40% in Australia [5].

Epidemiological studies have shown higher incidences of BC in those who are overweight or obese when compared to those of a healthy weight [6]. Obesity indicates a high percentage of body fat which has previously been an important predicting factor for both cancer incidence, and prognostic outcomes; however, emerging research suggests that fat free mass (weight the of body excluding weight of fat [7]) is a greater predictor of prognostic outcomes [8].

Apart from obesity being a risk factor for BC, it is common for women with BC to experience a loss in muscle mass, and/or gain in fat mass post diagnosis [8, 9]. Weight gain in patients with BC, particularly those who are premenopausal or undergoing chemotherapy, is a phenomenon that has been reported since 1978, and in 2001, Demark-Wahnefried *et al* reported that weight gain during adjuvant chemotherapy was associated with decreased muscle mass and an increase in fat mass simultaneously (sarcopenic obesity) [10, 11]. Sarcopenic obesity is associated with poorer prognostic outcomes [8, 9].

Despite the abundance of research in early stage BC, little is known of the effects of chemotherapy on body composition in patients with metastatic BC. To our knowledge, the only study investigating body composition changes in patients with metastatic BC was conducted by Rier *et al* in 2017. This retrospective study reviewed 98 patients with metastatic BC from 2000-2006, and found through their routine pre- and post-treatment CT scans that, the quality of muscle (muscle attenuation) decreased with paclitaxel chemotherapy treatment, while adiposity and muscle mass remained stable [12]. An unpublished systematic review exploring exercise interventions for metastatic patients with BC has found a total of seven Randomised Control Trials (RCTs), however none of these studies included body composition as an outcome [13].

With little known about the metastatic BC population, current practice for this population group is not influenced by high quality, recent evidence; therefore, limiting optimal outcomes for patients with metastatic BC. The current research study aims to investigate the effects of chemotherapy on body composition and physical function in women with metastatic BC.

This thesis includes 4 chapters; the current introduction, a review of literature, a research study manuscript, and conclusions and recommendations. These chapters will provide insight into the purpose of this research; explore current literature and associated gaps with a literature summary matrix table available in *Appendix A*; as well as a detailed research study; preliminary results; and future recommendations. The current chapter highlights the importance of research in this area of metastatic BC. The following chapter summarises the available research on body composition and BC, explores changes in body composition during treatment and how that may affect physical function, outcomes, and prognosis. The third chapter will include the preliminary results of the research study, while the final chapter will explore future recommendations based on the previous chapters in this thesis.

PART 2.0 Literature Review

2.1 Breast Cancer

2.1.1 Prevalence and Outcomes of Cancer

Cancer is the second highest contributor to non-communicable disease deaths worldwide, and in 2018, 138,321 new cancer diagnoses are expected in Australia [1, 14]. Not only is cancer one of Australia's leading causes of death, but the social and economic burden to individuals, families, and communities is considerable [15].

In women, Breast Cancer (BC) is the most common type of cancer. BC contributes to approximately 25% of all cancer cases world-wide, and while both males and females are affected by BC, being female is the single biggest risk factor to developing the disease [8, 9]. Next to this, an increased age, significant family history or genetic predisposition to BC, and being overweight or obese are also strong risk factors [9].

There are several stages of BC which influence treatment plans, and prognosis [4]. Early stage BC describes tumours that are no more than two centimetres and have not spread to the surrounding tissue or lymph nodes; locally advanced BC describes tumours that have spread beyond the breast to surrounding tissue or lymph nodes surrounding the breast [4]. Metastatic BC is defined as when the disease is no longer localised to the breast, and has spread to other organs in the body [9]. Often, metastatic disease affects women who have had a previous diagnosis of BC, however for some women, it may be their first diagnosis[4, 5].

While BC is a highly prevalent disease, with treatment, there is also a high survival rate for primary stages of the disease [8]. Five-year survivorship rates of primary BC are approximately 90% in Australia, and have improved from 72% in the 1980's [8]. Despite this, the rate of women in Australia who survive at least five years post metastatic BC diagnosis is 40% as of 2016 [8]. In general, higher survival rates are more common in higher-income countries where prevention measures such as early screening, and well-established treatments are accessible [8], however the patient's quality of life varies based on a number of influencers such as age, partnership status, and financial resources [16].

Having a high incidence within many communities around the world, it is clear why BC is one of the most studied malignancies [8]. However, despite the abundance of research that is available for primary BC, a recently conducted systematic review found only 7 papers investigating physical exercise interventions in

the metastatic BC population and no studies investigating nutrition interventions [13]. This review reinforces the gap in knowledge surrounding body composition and associated impacts for this population.

2.1.2 Treatment, Associated Symptoms and Effects on Body Composition

Treatments for BC differ depending on the progression of the cancer, the individual's overall health, age, the molecular make-up of the individual tumour, and gene expression. Treatments can include one of, or a combination (adjuvant) of surgery, radiation therapy, chemotherapy, or hormone therapy [4]. Treatment goals for primary BC (early stage to locally advanced) are to eradicate the tumour and prevent it from returning; whereas the goal for treating metastatic BC is to maintain quality of life, prolong life, and to reduce symptoms and pain [4].

Treatments often coincide with related side effects, and depending on the individual, type, and duration of treatment, side effects may be chronic and/or acute, however this varies with each treatment and each individual patient [17]. Common short-term side effects of chemotherapy can include anything from: nausea; fatigue; decreased immune function; pain; neuropathy; dry mouth; vomiting; metabolic, psychological and emotional disturbances; hair loss, dyspnoea, mucositis, diarrhoea, muscle weakness, osteoporosis, and/ or wound infection [4]. Similar symptoms present with radiotherapy and vary depending on the location of radiation; skin irritation, dryness, itching, blisters, and peeling; fatigue; scarring of organ tissues and joint stiffness are general side effects of radiotherapy [17, 18]. Possible side effects from surgical treatment include pain, discomfort, wound infection, bleeding, lymphedema, and or blood clots; complications during surgery are often minor and are easily treated [17, 18]. These treatment-related side effects may cause altered eating habits, which may contribute to either weight gain or loss, influencing changes in overall body composition [17]. While chemotherapy-related side-effects are often only experienced during treatment, some patients may suffer from long-term side-effects [19]. Certain chemotherapy drugs may cause long term damage to organs such as the lungs, or heart, and cause fatigue, low immunity, and/or infertility in some patients [19].

The most common drugs used for metastatic BC are either anthracycline- or taxane-based for palliative intent [20]. These treatments may lead to side-effects such as nausea, vomiting, diarrhoea, and anorexia (loss of appetite) [20]. Additionally, anthracycline- and taxane-based treatments have been associated with a decline in muscle quality [12], however only one known human study investigated the

changes in body composition with anthracycline- and taxane-based treatments in metastatic BC. Therefore, further research on the effects of chemotherapy on muscle quality is required.

2.2 Body Composition and Physical function

2.2.1 Outcomes Influenced by Body Composition

Traditionally, the weight to height ratio, also called Body Mass Index (BMI) has been a common tool used to aid in calculating risk for chronic disease [21], however, body composition may give a clearer understanding of someone's health outcomes when compared to BMI [22]. Body composition refers to the percentages of fat mass, lean body mass, and bone in an individual's body [23]. An unfavourable body composition aligns with a high body fat percentage, and/or low lean body mass percentage, with or without the presence of a high BMI [24]. High body fat percentage and low lean body mass, also called sarcopenic obesity, is associated with cancer risk and tumour progression [25, 26]; and while this is not completely understood, mechanisms involving chronic inflammation, insulin resistance, low adiponectin levels, and increased endogenous sex steroids associated with a high body fat are the most studied [25, 26].

In addition to cancer risk and tumour progression, a low muscle mass is associated with further adverse outcomes such as increased falls risk, poor physical function, and negatively impacting quality of life in older populations with age-related decreased muscle mass [27]. A strong association with physical disability (loss in physical function and declined muscle strength) has been observed in participants with a muscle mass at least two standard deviations below the relevant reference cut offs [27]. While the associations between a decreased muscle mass is well established, it is becoming increasingly recognised that a decrease over time in muscle mass is a greater predictor of future outcomes when compared to muscle mass alone [27].

2.2.2 Body Composition and Cancer

It is not uncommon for patients with BC to experience changes to their body composition post diagnosis [11]. Patients undergoing adjuvant chemotherapy commonly experience treatment-related symptoms of loss of appetite, nausea, and vomiting which are often associated with weight loss [18]. Dixon *et al* first observed a unique change in body composition of patients with BC in 1978, whereby

patients would gain weight despite experiencing nausea and vomiting [10, 28]. In the years following Dixon *et al*, weight gain in the BC population became a common observation, with weight gain ranging between 2.5 - 6.2kg in 12 months [10, 28, 29].

Adjuvant chemotherapy associated weight gain has previously been attributed to a positive energy balance (state of which the body has gained more energy than it has spent) [10]. However, recent studies have shown that there are more factors other than positive energy balance, which affect weight gain in this population, such as insulin resistance; physical inactivity (regardless of energy intake); and menopause-like hormonal changes that impact fat metabolism [10, 30]. Although there is limited research, evidence suggests that patients with BC either gain fat mass, lose lean body mass, or experience both during adjuvant chemotherapy treatment [10].

Demark-Wahnefried and colleagues observed weight changes in 60 patients with BC (n=38: adjuvant chemotherapy, n=22: localised treatment) at four time points (baseline, 2 months, 6 months and 12 months) and assessed weight, body composition, resting energy expenditure, physical activity, energy intake, and monthly 2-day dietary recalls [10]. Findings highlighted that a decrease in physical activity as the most likely factor contributing to adjuvant chemotherapy weight gain, and that weight gain can occur either with or without lean tissue loss [10].

Contrast to Demark-Wahnefried *et al*'s findings, Kutynec *et al* found only small shifts in body composition over 12 weeks (-0.4kg LBM, + 1.3kg FM) in both localised treatment (n=10) and adjuvant chemotherapy (n=8) treatment groups [31]. As this study followed up after only 12 weeks, it is likely that larger body composition shifts would be observed after a longer time period.

The aforementioned studies have been researching early stages of BC. Further research is required, as there is no research currently investigating these relationships in the metastatic BC population.

2.2.3 Breast Cancer and Body Composition Changes: influence on outcomes

Weight gain in women with BC may have many physical, social, emotional and psychological impacts [10] that has been reported as "distressing" by some patients [11]. For some patients, increased weight not only impacts one's quality of life, it affects the individual's general health, and prognostic outcomes [32].

Weight gain and adiposity has been associated with increased mortality and disease recurrence in women with early stage BC [33, 34], while also increasing risk of obesity related complications such as diabetes, hypertension, and cardiovascular or gall bladder disturbances [10].

2.3 Sarcopenia

2.3.1 Definitions of sarcopenia

Sarcopenia is an age-related involuntary loss of skeletal muscle mass associated with loss of physical function, frailty, and disability [35, 36]. The condition is most common amongst individuals over 80 years of age, and affects approximately 20% of individuals over 60 [37]. These percentages however, are likely to be underestimated as participation of frail or institutionalised individuals in these age groups is often low in clinical trials [37]. Age-related loss in muscle mass is the primary cause of sarcopenia in geriatric populations [22], however suboptimal diet, bed rest, sedentary lifestyle, chronic diseases, and medications or treatments will also influence the progression of sarcopenia regardless of age [22, 36].

It is common to see an age-related gain in fat mass in combination with a decline in muscle mass, however this shift in body composition may also be influenced by aforementioned factors. A body composition of low muscle mass and high fat mass in the presence of decreased muscle strength and/or physical function is known as sarcopenic obesity [38]. Sarcopenic obesity can occur in the presence of a high, normal, or low BMI, and is of greater concern than sarcopenia without obesity, as it has been found to be associated with poorer muscle quality (ratio between muscle quantity and strength) and strength [38]. A study exploring the force per unit of cross-sectional muscle area in obese elderly, non-obese frail, and normal weight, non-frail participants found that although obese elderly participants had the highest quantity of muscle, they had the poorest muscle quality when compared to other participant groups [38]. In the same study, obese elderly participants also had reduced functional status, aerobic capacity, walking speed, balance, and strength when compared to other participants [38, 39].

While no broadly accepted clinical definition exists for sarcopenia, the European Working Group on Sarcopenia in Older People (EWGSOP) recommends using the presence of both low muscle mass and low muscle function (muscle strength or physical function) for the diagnosis of sarcopenia [22]. Sarcopenia is a condition that has many attributing causes and outcomes, and is recognised as a multi-faceted condition with varying levels of severities and relative disease stages[22, 36]. The EWGSOP has developed conceptual

stages of sarcopenia to aid in diagnosing disease severity (Table 1) [22]. Conceptual staging of disease can guide clinical management and treatment of sarcopenia, and may assist future research studies [22].

Table 1: Conceptual stages for sarcopenia [22]

Stage	Muscle mass	Muscle strength	Physical function
Presarcopenia	↓		
Sarcopenia	↓	↓	Or ↓
Severe sarcopenia	↓	↓	↓

Defining reference values for sarcopenia depends on measurement techniques, equipment, and availability of reference studies. The EWGSOP recommends using normative (healthy young adult) data over predictive populations with cut-offs at 2 standard deviations below the mean reference value [22]. This being said, the majority of studies that have been used to develop reference values lack ethnic diversity and include mostly Caucasian participants [40]. Further research involving world-wide populations and ethnicities is required to obtain more accurate reference values [40].

2.3.2 Sarcopenia and Cancer

While weight gain has traditionally been a predictor for disease outcomes in BC, emerging evidence exploring the relationship between fat and lean body mass has highlighted the importance of skeletal muscle stores in improving cancer outcomes [41]. In cancer patients, low lean body mass, or sarcopenia, is associated with treatment failure, increased chemotherapy toxicity, and overall survival irrespective of adiposity [41]. A systematic review investigating the prevalence of pre-therapeutic sarcopenia in cancer patients found that sarcopenia was present in 38.6% of 6894 participants, and was significantly and independently associated with post-operative outcomes, chemotherapy related toxicity, and reduced survival [42].

In 2009, Prado and colleagues found sarcopenic patients with metastatic BC had increased chemotherapy toxicity ($p=0.04$), and shorter time to tumor progression when compared to their non-sarcopenic counterparts (62 days and 105 days respectively) [24]. These findings were supported by additional studies exploring the same outcomes in cancer patients [43, 44].

Recently, sarcopenic obesity has been associated with worse clinical outcomes for cancer patients [45]. A review of 14 studies involving clinical outcomes of sarcopenic obesity in cancer patients found that sarcopenic obesity was highly prevalent amongst the cancer population, and negatively affects prognosis [45]. The included studies in the review had heterogeneity in methods to categorise sarcopenia, therefore limitations apply; nevertheless, results showed that sarcopenic obese participants had an increased chance of postoperative complications (5-fold increase), poor functional status (47% of sarcopenic obese participants opposed to 27% non sarcopenic obese), and shorter survival (11.3 months opposed to 21.6 months in obese participants with normal muscle mass) when compared to non-sarcopenic obese participants [45].

2.4 Exercise in Cancer

2.4.1 Background, Current Research and Guidelines

Exercise has proven to be an integral part of a healthy lifestyle and if practiced regularly, is able to alter one's body composition by increasing muscle mass and reducing fat mass [46]. In cancer, it has now been well documented that exercise interventions are safe, improve physical function, disease outcomes and overall quality of life through an increase in muscle mass [47].

A systematic review and meta-analysis investigating the effects of resistance training exercise on muscular strength in cancer patients undergoing treatment found that resistance exercise was effective in improving lower-limb muscle strength, maintaining lean body mass, and reducing body fat; supporting resistance training exercise [48]. In BC however, Holmes *et al* reported that aerobic exercise training in women with primary BC had a protective association: women in the study who exercised greater than nine hours each week had reduced risk of recurrence, cancer-related mortality, and overall mortality [49]. Courneya and colleagues investigated the effects of aerobic exercise training and resistance training exercise in patients with BC undergoing adjuvant chemotherapy. Results from this study found that resistance training exercise was superior to usual care and improved self-esteem, muscular strength, lean body mass percentage, and chemotherapy completion rates [50]. While there were positive changes in quality of life, fatigue, depression and anxiety in both aerobic and resistance training exercise groups compared to usual care, these outcomes did not reach statistical significance [50].

Currently, general recommendations suggest that cancer patients participate in 30 minutes of moderate exercise (either resistance or aerobic), 5 days a week (150 minutes per week) [51]. These recommendations are based on research showing improvements in mood, fatigue, and osteoporosis with exercise, as well as favourable survival outcomes and lower rates of adverse side effects [51, 52]. This guide to exercise is a general recommendation and will depend on individual circumstances, in which case, varying recommendations may be offered [51].

2.4.2 Exercise for Sarcopenia in Cancer

Several studies have investigated age-related sarcopenia, and interventions to delay disease progression and/or improve muscle mass by applying exercise interventions.

Exercise interventions for sarcopenia in older adults have proved beneficial and were reviewed by Taffe in 2006 [37]. Taffe noted that numerous studies [53, 54] demonstrated that resistance exercise training amongst older men and women improved muscle cross sectional area, and muscle strength significantly (>100%) when participating in a resistance exercise intervention for 12 weeks [54]. A systematic review of low-quality randomised controlled studies investigating exercise, dietary, and drug interventions for treating sarcopenia alone, found that 3 months of resistance exercise interventions (2-3 times per week) may play a role in improving muscle mass, muscle strength, and walking speed in older individuals with sarcopenia [55].

Limited studies have been conducted investigating exercise interventions specifically for cancer patients with sarcopenia. However, a RCT conducted in 2012 investigated the impact of resistance and aerobic exercise training on sarcopenia, and dynapenia (reduced strength) in patients with BC receiving adjuvant chemotherapy [53]. The study reported that resistance training exercise was superior to usual care in improving sarcopenia-related outcomes, and when compared to aerobic exercise training and usual care, resistance exercise training was superior in reversing sarcopenia [53]. More research on the effectiveness of exercise interventions in sarcopenic patients with metastatic BC is required.

2.4.3 Barriers to Physical Exercise

The profound improvements that exercise has on muscle hypertrophy and strength, particularly with resistance exercise training, are well known, however barriers to physical exercise still exist within both

healthy and unwell populations. A 2012 survey conducted by the British Heart Foundation found that the most common barriers to exercise for UK healthy adults were work commitments (45% men, 34% women), and time (38% men, 37% women) [56]. Despite evidenced-based guidelines and well supported positive outcomes, cancer patients are not meeting the recommended amount of physical exercise, and are therefore not experiencing the potential benefits of exercise. A study conducted in 2014 in the UK observed the physical activity levels and barriers to exercise in 114 patients with either bowel, breast, or prostate cancer. The authors found that 76% of patients did not meet exercise guidelines of 150 minutes per week, and of those patients eligible for exercise referral, 44% refused. The main barriers to physical exercise in these patients were health concerns (32%) and time (27%) [52].

A RCT explored the change in patient-perceived exercise barriers in prostate and breast cancer survivors at baseline, and after 1 year of being on a home-based exercise and healthy eating intervention [57]. At baseline, 52% of participants with BC and 45% of participants with prostate cancer reported "too busy" as the top barrier to exercise, while "no willpower", and "don't like exercising in bad weather" were also in the top three reported barriers [57]. At 1 year, the number of participants recording these barriers had reduced by 37% and 36% in the breast and prostate cancer survivor populations respectively [57].

A 2014 study focus group investigated factors that influenced exercise adherence in patients with BC and highlighted both internal and external barriers to exercise in this population [58]. The study involved 27 patients with BC in a home-based exercise program that combined both resistance and aerobic exercises. Participants were also asked questions on their perceptions and experiences in engaging with the exercise program to explore barriers and adherence. Valuing other activities over exercise, and treatment side-effects were the two barriers that were highlighted by the focus group [58]. Participants also expressed that their desire to restore normality in life, constructive support during exercise, and the positive outcomes that come with exercise as motivators to participate in the exercise program [58]. In conclusion, time, and health concerns are reoccurring barriers to physical activity in the BC population; this may be due to limited education regarding the positive outcomes of exercise during treatment, and poor access to exercise programs for this population.

2.5 Dietary Interventions for Cancer and Sarcopenia

2.5.1 Diet, Muscle Growth and Maintenance

Muscle maintenance and growth can only occur if muscle protein synthesis occurs at a greater rate than muscle protein breakdown; this requires a positive protein balance and results in higher muscle tissue turnover [59]. Dietary protein is essential for muscle maintenance as it provides amino acids that are required for muscle protein synthesis. Exercise with reduced protein intake results in a negative protein balance, which causes muscle catabolism [60]. Maintenance of muscle requires a balance of anabolic and catabolic states within the muscle tissue, a balance that, with age, favours muscle breakdown [61, 62]. In sarcopenia, there is a decreased sensitivity of protein synthesis, and a loss of physiological concentrations of amino acids due to a lack of cell-signalling pathway (mTOR) activity, which causes a negative protein balance and muscle loss [60].

2.5.2 Current Research on Diet, Sarcopenia, and Cancer

Dietary intervention studies for sarcopenia in patients with cancer is not well documented. A systematic review by Yoshimura *et al* suggests that although this is based on low-quality evidence, nutritional intervention through essential amino acids, collagen peptides, protein, Vitamin D, beta-hydroxy-beta-methylbuterate, leucine, branched-chain amino acid, creatine and tea catechin supplements (not combined) may play a role in improving muscle strength over 3 months of intervention in patients with cancer? [55].

A systematic review investigating the use of nutritional, vitamin and mineral supplements as treatment for cachexia in cancer patients evaluated 21 papers [63]. The review found that vitamin D and vitamin C (oral and intravenous (IV)) supplementation improved muscle strength, and physical and cognitive domains of quality of life in cancer patients [63]. In terms of protein and dietary supplements, three studies observed positive effects on weight gain of combining arginine, glutamine, and beta-hydroxyl beta-methyl butyrate [63].

In summary, while research in the domain of dietary supplementation is limited in sarcopenic and cachexic cancer populations, some promising results highlight the need for further investigation into these relationships to improve current guidelines.

2.5.3 General Nutrition Guidelines for Cancer Patients

Previous research exploring diet and exercise in cancer patients has led to a set of lifestyle recommendations for cancer patients. The 2012 Australian evidence-based practice guidelines for patients receiving chemotherapy and/or radiation therapy suggest dietetic interventions (nutrition counselling, and /or supplements) to increase dietary intake and weight, but have little effect on patient-centered outcomes such as quality of life, physical function, and patient satisfaction [64]. In patients receiving radiation, aiming for at least 125kJ/kg/day and 1.2g/protein/kg/day was recommended [64]. Chemotherapy patients have effective results of improved dietary intake and weight through standard nutrition counselling and/or oral nutritional supplements [64].

The 2017 ESPEN guidelines on nutrition for cancer patients recommends that cancer patients have their nutrition status monitored regularly, with quantitative and objective measures of nutritional intake taken [65]. For patients with advanced/metastatic cancer, the ESPEN guidelines strongly recommend to routinely screen for adequate nutrition intake, and to tailor nutrition interventions if needed with the patient to consider disease progression, quality of life, and patient burden [65].

2.6 Conclusion of Literature

A thorough and critical exploration of the available literature highlights the knowledge gaps for exercise and nutrition in the metastatic BC population. Intervention studies involving early-stage BC populations and sarcopenic populations have proven exercise is beneficial for improving muscle quality, muscle strength, and physical function – therefore improving overall quality of life and outcomes. We also know there is evidence showing the benefits of nutritional counselling and supplements to improve muscle mass, however no clinical studies have been published investigating a combined nutrition and exercise intervention in metastatic BC. Further research into whether exercise has the same benefits in the metastatic BC population, in combination with nutrition interventions will provide evidence-based practice guidelines to enhance quality of life for these patients.

Part 3.0 Manuscript

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BODY COMPOSITION AND PHYSICAL FUNCTION DURING CHEMOTHERAPY FOR METASTATIC BREAST CANCER – A PILOT OBSERVATION STUDY

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Abbreviations: r.v.: reference value; QOL: quality of life; FFM: fat free mass; FFMI: fat free mass index; FMI: fat mass index; CT: Computed Tomography; PF: Physical Function; EWGSOP: European Working Group for Sarcopenia in Older People; MST: Malnutrition Screening Tool; PG-SGA: Patient Guided Subjective Goal Assessment

3.1 Abstract

Background:

The current scope of literature exploring body composition changes during chemotherapy has primarily been investigated in patients with early-stage (I-III) breast cancer (BC), with little known in patients with metastatic BC. A higher fat free mass index (FFMI) has been associated with improved treatment outcomes, survival, and quality of life in cancer patients. With the known benefits of a high FFMI in cancer populations, this study aims to describe changes in body composition, muscle strength, and physical function during chemotherapy in the metastatic BC population to inform future intervention studies for the improvement in overall quality of life.

Methods:

This was a 6-week prospective observational cohort study where we measured changes in FFMI, muscle strength, and physical function in patients with metastatic BC during chemotherapy. Quality of life, protein intake, physical activity, and malnutrition status were also measured. Values were compared to reference values (where applicable age- and gender specific).

Results:

Five participants were enrolled in the study, and three completed all measurements. Preliminary results did not indicate sarcopenia in any of the participants, however at baseline 3 participants were overweight or obese, median protein intake in all participants was below recommended intakes (75%), and 4 participants did not participate in the recommended amount of physical activity. Physical function did decline with time in 2 participants, and muscle strength remained stable in three participants that completed the study.

Conclusions:

From the preliminary data collected, our sample size reflects similar trends to those highlighted in early-stage BC populations. Most of our participants were overweight or obese, the median protein intake was inadequate, and participants did not participate in sufficient physical activity. Additional recruitment is required to confirm these trends in the metastatic BC population.

3.2 Introduction

Breast cancer (BC) is the most common type of cancer diagnosed in women, with approximately 8.2 million diagnoses of BC globally in 2012 [66]. Evidence suggests that patients with cancer typically experience involuntary weight loss due to treatment side-effects; however, patients with early stage (I-III) BC are more likely to experience a gain in fat mass, which in some cases, is accompanied by a simultaneous loss in muscle mass [67]. Low muscle mass in combination with a loss in function and, or muscle strength is known as sarcopenia [22]. This reduction in muscle mass in the presence of higher fat mass is known as "sarcopenic obesity" and may occur with or without the presence of a high body mass index (BMI) [68].

While obesity is generally considered a major body compositional predictor for poor health and disease prognosis, recent evidence suggests that a loss of muscle mass in the presence of a high fat mass is a greater predictor for negative health outcomes in both healthy, and cancer populations [22, 69, 70]. Sarcopenia is usually a chronic condition related to either age, lack of physical activity, nutrition (insufficient protein intake), or disease (for instance individuals with cancer, chronic obstructive pulmonary disorder (COPD), or chronic heart failure) and is accompanied by a decline in physical function and/or loss of muscle strength [22, 68, 71]. The decline in physical function and strength associated with sarcopenia affects an individual's independence, mobility and nutrition status [22, 68].

Body composition has been shown to influence not only BC risk, but also outcomes post treatment [70]. Whilst findings are unclear on exact numbers, moderate increases in dietary protein for elderly people with sarcopenia have been shown to improve lean body mass, strength and physical function [72-74]. This could be either achieved by protein intakes above the recommended intake or supplementation of amino acids or protein.

For muscle mass and physical function maintenance, general recommendations for patients undergoing cancer treatment are to consume sufficient dietary protein ($\geq$ 1.2g/kg (adjusted) body weight [75]) and to participate in physical activity [65, 76, 77]. While the benefits of exercise therapy for both sarcopenia and cancer are well explored to help preserve muscle mass; reduce fat mass and treatment side-effects; and improve strength, self-esteem, and overall quality of life [78, 79], the large majority (40-80%) of patients with BC or survivors are not meeting recommended physical activity levels [80-86]. In addition, BC survivors are unlikely to be meeting the recommended amount of dietary protein [87], however there is currently no data on physical activity levels and protein intake in the metastatic population. Moreover, research investigating body compositional changes in patients with BC exists primarily in early-stage BC, and there is currently no research investigating chemotherapy effects on body composition in the metastatic population.

Further research investigating body composition and chemotherapy in patients with metastatic BC is needed to provide evidence-based recommendations to improve physical function, strength, and overall QOL for this patient

group. The aim of this observational cohort study was to investigate the effects of chemotherapy on body composition, physical function and muscle strength in adult patients with metastatic BC in Australia. We also explored the relationship between body composition, physical function, and muscle strength. These aims were to inform future intervention studies for this population group.

3.3 Methods

3.3.1 Study Design

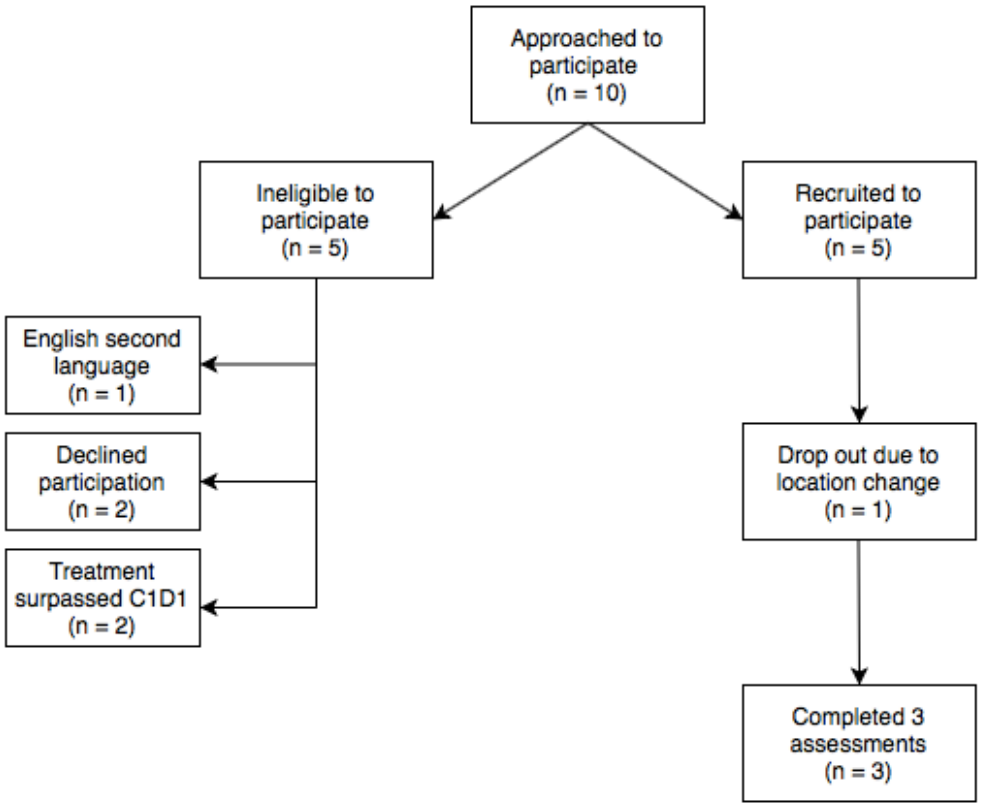
This prospective observational cohort study was reported according to the STROBE guidelines. Participants undergoing chemotherapy for stage IV BC were recruited upon enrolment of chemotherapy (Baseline: Cycle 1, Day 1 (C1D1), of chemotherapy), and assessed again at 3 weeks and at 6 weeks. A detailed time-line of the project is presented in Appendix B.

3.3.2 Eligibility criteria and recruitment

To be included in the study, participants were required to meet the following criteria; female; above 18 years of age; metastatic BC disease (primary); life expectancy greater than 3 months; mobile; ECOG performance status of 0,1, or 2 (confirmed by the participant's oncologist) [88]; commencing C1D1 of chemotherapy for metastatic BC where minimum 2 cycles of chemotherapy were scheduled; and able to speak, read and write English. Participants were to be excluded if they had a permanent pacemaker or other medical implant not appropriate for BIA assessment; severe cognitive, intellectual disability or mental illness; presence of acute illness or unstable chronic illness; or any other condition that would interfere with the study or safety of the patient according to the PI, nurse, or patient.

Participants were recruited from oncologist, nursing staff, and cancer care coordinator referrals at the Mater Cancer Care Centre (MCCC). The primary researcher (AB) would review upcoming appointments in the chemotherapy treatment scheduler system to acquire any potential participants, and confirm appropriate eligibility with oncologists and/or cancer care coordinators. The study was also announced by study flyers in waiting areas. Those who were interested in participating were screened for eligibility through inclusion and exclusion criteria. Of the 10 participants approached for the study, 5 were excluded and reasons for exclusion were recorded. Reasons for exclusion included English as a second language, did not wish to participate, did not classify as metastatic disease, and having already surpassed C1D1) of their chemotherapy. Participants that were eligible received a written and verbal explanation of the study by the PI or student investigator before consent was obtained. This study was approved by the Human Research Ethics Committee of Mater Research and Mater Research Governance (HREC/17/MHS/63) (Appendix C).

Figure 1 Flow chart of study recruitment



3.3.3 Participant Descriptive Characteristics

After written consent was obtained, the primary investigator recorded age, smoking status, and ethnicity of the participant during a face-to-face interview at the MCCC. Medical history, treatment regimen, and stage of disease were obtained from the participant's medical records. All information recorded was de-identifiable on the approved CRF, and then recorded into the database. Participants then completed baseline measurements on C1D1 of their treatment. Measurements involved anthropometric measures, body composition, muscle strength, physical function, dietary intake, and quality of life as described in Sections 3.3.4 to 3.3.6, and 3.3.9. Malnutrition and sarcopenia status were classified for participants post data collection as described in Sections 3.3.7 and 3.3.8.

3.3.4 Anthropometry

Height was recorded at baseline with each participant having taken their shoes off, arms hanging freely by their sides, using a stadiometer (Wedderburn WM303H, Willawong, QLD, Australia); measurements were rounded to the nearest 0.5cm and recorded in meters. Participants were weighed without shoes on calibrated scales at each time point in the study. Weight on a digital scale (Wedderburn WM303H, Willawong, QLD, Australia) was recorded to the

nearest decimal in kg and the participant's BMI at each time point was calculated by dividing weight (kg) by squared height (m^2).

3.3.5 Body Composition

Body composition was measured at each time point using a tetra polar (ankle-foot) lying multiple frequency bio-impedance analysis (BIA) device (Impedimed SFB7, Carlsbad, California, United States of America). Measurements were taken prior to placement of intravenous (IV) tube, and after the participant was lying down in resting position for 5 minutes. Participants were to remove all jewelry, metal objects and shoes. A user manual was developed by the research team to be followed in order to reduce measurement bias (Appendix D1). Fat free mass, fat mass, intracellular water, and extracellular water, were recorded into the participant database and expressed in kg, % of body weight, and kg/m^2 (FFMI and FMI). FFM index was compared to reference values by Gonzalez *et al* that were adapted from Kyle *et al's* cut offs [89] (Appendix E). FFM- and FM-index were calculated via the following equations:

$$FFMI = FFM\ (kg) \div (height\ (m)^2)$$
$$FMI = FM\ (kg) \div (height\ (m)^2)$$

3.3.6 Muscle Strength and Physical Function

Muscle strength was measured using hand grip dynamometry (JAMAR plus+, JAMAR, Hatfield, United States of America) at each time point using the non-dominant arm at 90 degrees; measurements were taken three times with standardised encouragement by the administer to provide a maximum and average score in kilograms; all three attempts were recorded. A user manual was developed for investigators to follow to reduce measurement bias (Appendix D2). Participant scores were compared to age- and gender specific reference values developed from 406 older subjects (283 females, mean age 76.6 years) based on the European Working Group for Sarcopenia in Older People's (EWGSOP) definition of sarcopenia [40].

Physical function was assessed using a 6-minute walking test (6MWT) performed by a trained administer at each time point. The 6MWT was performed on a flat, straight surface, 20 meters in length with standardised encouragement given at each minute. Blood pressure was measured prior to commencing the 6MWT to ensure the participant was fit to participate. Oxygen saturation and heart rate were measured using a ChoiceMMed sats monitor (ChoiceMMed Germany, Düsseldorf, Germany) and perceived exertion was measured using the revised category-ratio Borg scale every minute [90]. Limiting factors of the walking test reported by the participant were also recorded post completion. If the participant chose not to participate in the 6MWT, a 4-meter walking test was conducted (4MWT). For this test, the investigator measured 4 meters on a flat, straight surface and would record the time it took for the

participant to walk this distance meters as fast as possible. Physical function was assessed by gait speed (m/s) and compared to age- and gender specific reference values developed from 406 older subjects (283 females, mean age 76.6 years) based on the European Working Group for Sarcopenia in Older People's definition of sarcopenia [22]. Gait speed was calculated via the following equations:

6MWT: distance (m) ÷ 360 seconds (6 minutes) = gait speed (m/s)

4MWT: 4 meters ÷ time (seconds) = gait speed (m/s)

3.3.7 Definition of Sarcopenia

Participants were defined as presarcopenic, sarcopenic, or severely sarcopenic based on the definition recommended by the EWGSOP [22]. Sarcopenia was based on muscle mass (FFMI), muscle strength and physical function combined (*Table 1*). Sarcopenic obesity was defined if participants were classed as sarcopenic, with a FMI above the age- and gender specific reference cut off (Appendix E).

Table 1 Conceptual stages for sarcopenia [22]

Stage	Muscle mass	Muscle strength	Physical function
Presarcopenia	↓		
Sarcopenia	↓	↓	Or ↓
Severe sarcopenia	↓	↓	↓

3.3.8 Malnutrition Status

At each time point, malnutrition status of each participant was evaluated using the Malnutrition Screening Tool (MST) [91] and Scored Patient-Generated Subjective Global Assessment (PG-SGA) [92] tools by either an Accredited Practicing Dietitian or student dietitian. Each question on each tool was asked by the research investigator to give a numerical and categorical rating of malnutrition for the participant. The MST questionnaire gives a numerical score of from 0 - 4, 0 being no risk of malnutrition, and 4 indicating highest risk. The Scored PG-SGA gives an overall global assessment categorised into three ratings; A: well-nourished, B: mild to moderately malnourished, and C: severely malnourished. The Scored PG-SGA also gives a continuous numerical score from 0 to 55 which aids in calculating the global assessment; where a higher score indicates worse malnutrition signs and symptoms, and a score of 9 or more (7 or more in older adults) indicated critical need for dietetic intervention [93].

3.3.9 Physical Activity, Quality of Life and Dietary Recall

Participants completed a series of questionnaires at each time point in the study to assess their current physical activity levels, dietary intake, and quality of life.

Independent physical activity was measured using the Godin-Shepard Leisure-Time Physical Activity Questionnaire [94] to produce a numerical score of physical activity levels based on the amount of strenuous, moderate, or light exercise the participant part takes in over the previous week.

Quality of life was assessed using the EORTC QLQ-C30 questionnaire [95] which the participant completes prior to any other assessments, appointments, or treatments in order to produce an accurate score. The EORTC QLQ-C30 questionnaire is broken into five functioning scales (physical, role, emotional, cognitive, and social), three symptom scales (pain, nausea/vomiting, and fatigue), six single-item scales (dyspnea, sleep disturbances, appetite loss, constipation, diarrhea, and financial), and a global QOL assessment. Using an excel spreadsheet, participant's raw scores were appropriately transformed to a linear scale (0-100) where the higher score represents a higher functional level, or higher level of symptoms. Transformed scores were recorded into the de-identified database. Participant scores were compared to the European reference values for the EORTC QLQ-C30 as these reference values represent a general population reference for QOL in cancer patients [96].

Dietary protein and energy intake was determined using the five-pass dietary recall methodology to record a "typical" day of dietary intake of one weekday and weekend day. Energy and protein intake was assessed using the Xyris software in Foodworks ™ or Easy Diet Diary ™ programs. Dietary energy and protein intake analysed in the Xyris software was compared to the recommended protein and energy requirements based on NEMO guidelines of ≥125kJ/kg (adjusted) body weight, and ≥1.2g protein/ kg (adjusted) body weight for adults undergoing chemotherapy [75].

3.3.10 Data Analysis

This study was a convenience sample. To gain a well-rounded representation of this group, we aimed to recruit at least 45 eligible participants. This number was derived from the prevalence of sarcopenia in BC which is estimated to range from 25% [24] to 58% [97]. Using an average prevalence of sarcopenia of 40% and a potential dropout rate of 20%, 45 participants was required to be able to identify 15 participants with sarcopenia. This sample size would allow for comparisons to be drawn between groups and time points, and to investigate correlations between body composition and physical function.

Recruitment returned a small convenience sample, which influenced the initial data analysis plan. As only 5 participants have been included for baseline data, no normality testing was performed, and descriptive statistics were

presented as median and range (continuous), or by a number (categorical). Although recruitment returned a small number of participants, a data analysis plan has been outlined for further recruitment and is detailed below.

For future analysis, normally distributed continuous variables (age, height, weight, BMI) will be described by mean and standard deviation (not-normally distributed: median and IQR), while categorical variables (gender, stage of disease, use of oral steroids, independent exercise, ethnicity) will be described by number and percentage of total. Normality is tested using a Shapiro-Wilk test on continuous baseline and outcome variables. Continuous outcome variables (body composition, muscle strength, physical function, dietary intake, physical exercise, EORTC-QLQ-C30) will be analysed using a paired t-test between baseline and week 3, baseline and week 6, and week 3 and week 6. A paired t-test was chosen over a repeated-measures ANOVA as this testing requires no missing data points. Confounding variables of age, protein intake, and independent exercise will be tested using linear or logistic regression in the case of exceeding 20 participants. Associations between muscle strength and other variables will be analysed through a Pearson's correlation test. All data points will be taken into account, and in patients who dropped out, their data until attrition will be included in analysis.

3.4 Results

Within the preliminary 5-month recruitment time frame from November 2017 to March 2018, 10 women with primary metastatic BC were approached to participate in the study. Of these women, 5 were recruited for participation, 2 declined due to no desire to participate, and 3 were ineligible due to English being of second language, and having already surpassed C1D1 of their treatment (Figure 1).

Baseline characteristics are outlined in *Table 2*. The median age of participants was 62 years (range 47 - 76 years). At baseline, 4 of the 5 participants were categorized as well nourished, and 1 as moderately malnourished using the PGSGA malnutrition tool. Protein and energy intakes were insufficient in 3 participants. The median BMI of participants at baseline was 27kg/m^2; 3 participants were classified as overweight (n=2) or obese (n=1) while the remaining 2 were within the healthy weight range (BMI = 18.5-24.9). No participants were classified as sarcopenic at baseline based on their FFMI and physical function, or muscle strength. The Godin-Shepard Time Leisure question reflected that 4 participants did not engage in sufficient physical activity at baseline.

The QOL transformed global, and physical function scores from the EORTC QLQ-C30 questionnaire on baseline, week 3, and week 6 are displayed in *Table 3*. At baseline, the median QOL global score was 58.3 (ranging from 16.7 – 100), while the median physical function score was 73.3 (ranging from 60 – 80). Both median global QOL and physical function scores at baseline were above the median reference values (50 and 60 respectively) for women with BC stages III-IV.

Three subjects completed the study (*Table 3*). The first subject was a 70-year-old Caucasian female undergoing daily oral chemotherapy (Capecitabine). Although she was obese (BMI of 33.3kg/m^2), her FFM-index did not indicate sarcopenia. No significant changes were recorded in weight, body composition between baseline and week 3; due to equipment malfunctions, body composition could not be recorded on the final week 6 visit. The subject had a normal hand-grip strength and physical function a relatively high fat mass and insufficient physical activity. Global QOL for this subject decreased over time, however she was above the reference value for global QOL.

The second subject was a 62-year-old Asian female undergoing weekly IV chemotherapy (taxane-based). While FFMI, muscle strength, and physical function did not indicate sarcopenia, a BMI of 24.5 indicated normal weight. This subject had no significant changes in muscle strength, physical function, insufficient physical activity or weight over the 6 weeks, however her FFM-index dropped by 2kg/m^2 between baseline and week 3 but remained fairly stable between week 3 and week 6. FFMI did not fall below the minimal reference value for this subject. QOL remained stable at all time points, however was below the reference value.

The third subject was a 47-year-old Caucasian female undergoing IV chemotherapy (taxane-based) 3 weeks on, 1 week off. Physical function and muscle strength were normal, and there were no significant changes in weight or FFMI over time. FFMI, muscle strength and physical function did not indicate sarcopenia. At week 6, the participant's physical function decreased below the reference cut-off value. Physical activity was sufficient at baseline and week 3, however dropped significantly at week 6. QOL increased at the final time point, however was still below the reference value.

Table 2 Demographics and clinical characteristics of participants with metastatic breast cancer (n=5)

Characteristic	N
Age (years), median (range)	62.2 (47 – 76)
Ethnicity	
Caucasian	3
Asian	1
Pacific Islander	1
Smoking Status	
Yes	0

No	5
Treatment Pathway	
Oral	1
Intravenous	4
Chemotherapy Agents	
Taxane	2
Anthracycline	2
Capectabine	1

Table 3 Body composition, handgrip strength, physical function, sarcopenia and malnutrition scores of patients with metastatic breast cancer undergoing chemotherapy at baseline (n = 5)

Characteristic	Median	Range
Height (m)	1.63	1.58 – 1.67
Weight (kg)	72	61.0 – 92.7
BMI (kg/m^2)	27	22.8 – 33.3
FFM-index (kg/m^2)	18.74	15.4 – 20.4
FM-index (kg/m^2)	8.1	5.4 - .7
Sarcopenia (*n*)	0	
Handgrip Strength (kg)	25.6	18.7 – 32.4
Handgrip Strength (*n* below r.v. for sarcopenia)	0	
Physical Function (m/s)	1.1	0.97 – 1.3
Protein intake (% of requirement)	75%	40 - 115
MST score	1	0 - 2
0 (*n*)	3	
1 (*n*)	0	
2 (*n*)	2	

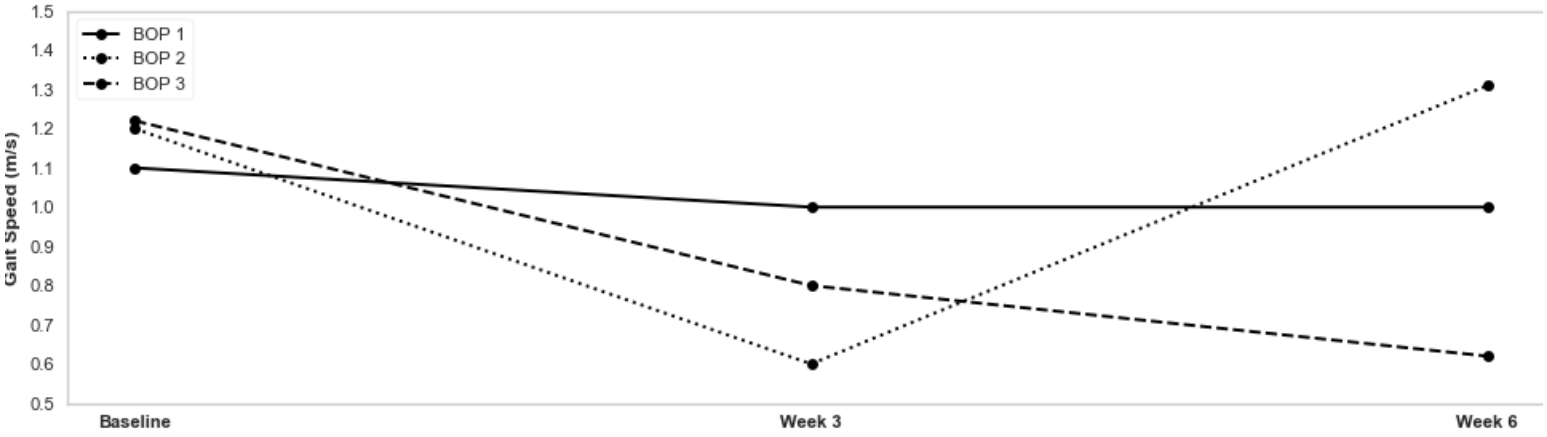
PG-SGA A (n, %)	4	
PG-SGA B (n, %)	1	
PG-SGA C (n, %)	0	
PG-SGA numerical score	6	2 - 12

Table 4 Descriptive and physical characteristics on three time points of chemotherapy in subjects/patients with metastatic breast cancer (n=3)

Parameters	Baseline	Week 3	Week 6	Reference Values (rv) Mean±SD
Global QOL score (% of rv)				
BOP_01	100	83.3	66.7[2]	58.2 ± (25.6)
BOP_02	33.3	33.3	33.3	62.2 ± (24.4)
BOP_03	16.7	16.7[1]	33.3[2]	61.3 ± (24.5)
PF QOL score (% of rv)				
BOP_01	60	66.7	73.3[2]	69.5 ± (23.9)
BOP_02	73.3	46.7	73.3	76.9 ± (21.6)
BOP_03	73.3	80[1]	93.3[2]	81.1 ± (19)
Weight (kg)				
BOP_01	92.7	92.7	92.4[2]	
BOP_02	68.3	68.2	67.8	
BOP_03	60.9	60.9[1]	61.5[2]	
FFMI kg/m^2 (% of rv)				≥ 15
BOP_01	20.4 (136%)	20.5 (137%)		
BOP_02	19.1 (127%)	17.1 (114%)	17.4 (116%)	
BOP_03	15.4 (103%)	15.6 (104%)[1]	16.2 (108%)[2]	
FMI kg/m^2				≤ 11.8
BOP_01	12.7	12.8		
BOP_02	5.4	7.4	7	
BOP_03	7.3	7.2 [1]	6.8[2]	
Muscle Strength kg (% of r.v.)				
BOP_01	28.7 (136%)	28.2 (134%)	31.7[2] (151%)	≥ 21 kg

BOP_02	21.3 (123%)	24.9 (144%)	26.3 (152%)	≥ 17.3 kg
BOP_03	26.8 (158%)	23.7[1] (139%)	28.9[2] (170%)	≥ 17
Exercise Score				≥ 24
BOP_01	8	26	18[2]	
BOP_02	5	9	6	
BOP_03	54	52[1]	14[2]	
Sarcopenia (y/n)				
BOP_01	no	no	n/a	
BOP_02	no	no	no	
BOP_03	no	no	no	

Figure 2 Change in physical function (m/s) over time



3.5 Discussion

Preliminary findings from this study have shown that in our small sample size (n = 5), there was no evident sarcopenia, a low rate (n = 1) of malnutrition, and a high rate (n = 3) of overweight and obesity. Muscle strength remained stable in the participants (n = 3) that completed the study, while physical function declined over the duration of the study in 2 participants. Insufficient protein intake and physical activity were noted in 4 out of 5 of the participants at baseline. For two of three subjects that completed the study, global quality of life scores were below reference cut-offs for the entire duration of the study, however, their physical function scores were within reference cut-offs at all time points, except one time point for subject 2. Subject 1's global quality of life score decreased, whilst their physical function score increased over the duration of the study; both scores, despite changing, remained within reference cut-offs.

Initiation of this pilot study was due to the limited range of research available exploring body composition, physical function, and muscle strength in patients with metastatic BC undergoing chemotherapy, creating a demand for evidence-based guidelines aimed at this population group. Although results from this study are preliminary, low physical activity levels and inadequate levels of protein intake highlighted within the study population are indicative of the lack of exercise and dietary protein. At present, online resources available for Australian patients with metastatic BC encourages "regular light exercise such as walking, swimming or gardening" and "a healthy balanced diet from the 5 core food groups" with no specific recommendations regarding the amount of exercise and dietary energy, protein other nutrients or foods [98].

While conclusions from research investigating early stage (I – III) BC populations cannot be directly transferred to the metastatic BC population, these studies have highlighted the importance of body composition's influence on outcomes of disease [25-27, 41]. Knowing that nutrition (in particular protein intake) and exercise influence body composition (particularly FFM and FM), it is concerning for participants in our preliminary sample population as they are mostly overweight or obese and exhibit lifestyle factors that are precursors to developing sarcopenia (poor protein consumption and low physical activity). As highlighted in Prado *et al*'s work, sarcopenic obesity was an independent predictor of survival in cancer patients, irrespective of age, sex and functional status [43].

The negative outcomes of sarcopenia have been extensively researched in cancer populations, and its associations with chemotherapy toxicity and treatment failure are well known [41, 42]. Exercise interventions in early stage BC populations, and other cancer populations highlight the benefits that exercise (particularly resistance training) can have on muscle mass, and therefore treatment outcomes, making a strong case for investigations to begin exercise interventions in metastatic BC populations [53-55]. Our study sample reflects the norm regarding physical in-activity in both cancer and healthy populations; Yang *et al's* study reported that 76% of 114 early-stage bowel, breast or prostate cancer patients did not meet the recommended 150 minutes of exercise per week [52], while a 2014 study investigating exercise barriers in 27 patients with BC highlighted both internal and external barriers such as valuing other activities over exercise, and treatment side-effects [58]. It would be useful for future studies involving metastatic BC populations to investigate barriers and enablers of physical activity, as well as involving exercise-monitoring devices to measure true physical activity levels; these outcomes may will provide a more accurate representation of physical activity in this group, and insights into perceptions of exercise.

Our study had several limitations, the first being a small sample size meaning we were unable to reach power, and unable to reflect true incidence of sarcopenia in this population. The small number of enrolled participants reflects the challenges that come with recruiting a strict inclusion criteria, in a restricted recruitment phase of 5 months. Our sample was restricted to patients with metastatic BC beginning a new cycle of chemotherapy treatment so that baseline measurements could begin on day one of the new cycle. This restriction made it difficult to recruit participants, and

further studies may choose to consider including participants who are at different stages of their first chemotherapy cycle for recruitment purposes. Further limitations regarding our small preliminary sample size meant that we were unable to use our own population sample as reference cut-offs for FFMI, and FFM as recommended by the EWGSOP [22]. Secondly, our study was limited with the follow-up time frame of 6 weeks; greater body compositional shifts would likely be more evident after a longer time period. This limitation will be overcome in future recruitment of the study with follow-up extended to at least 6 months. Plans for further recruitment for this study are in place to gain a greater understanding of the disease burden in this population to assess whether future lifestyle interventions are appropriate considering potential physical and social burden from participation.

3.6 Conclusion

Treatment goals for metastatic BC are palliative and focus on maintaining quality of life, prolonging life, and reducing treatment associated symptoms and pain [4], however, there is limited research that is aimed at improving current care nutrition and exercise guidelines for the metastatic BC population. With the ever-changing outcomes and survivorship for the metastatic BC population, evidence-based guidelines which are aimed at providing care that will enhance the remainder of their lives is a pressing task. Preliminary results from this study have found that this population face similar challenges to patients with early-stage BC of, insufficient physical activity, insufficient protein intake, and overweight and obesity, however no sarcopenia was identified. Additional findings from this study past preliminary results will give further insight into the prevalence of sarcopenia in this group and influence future intervention studies. Future observational studies may find value in investigating nutrition and exercise knowledge of the metastatic BC population as well as associated barriers and enablers to exercise. Investigating knowledge, barriers and enablers will give researchers a better understanding of how to structure intervention studies in this population group looking forward.

PART 4.0 Conclusions and Recommendations

This thesis highlights gaps in current literature regarding the effects of chemotherapy on body composition, physical function, and muscle strength in patients with metastatic BC, and emphasises the importance of moving forward to create evidence-based guidelines for this population (Parts 1 & 2). Extensive literature exploring these outcomes in early stage (I-III) BC has informed practice to improve treatment outcomes, and overall survival in this group, however the metastatic population has received minimal research attention perhaps due to the increased burden for metastatic disease.

The main goals for treatment in this population are to maintain quality of life, prolong life, and reduce treatment associated symptoms. Treatments for metastatic BC are ever-improving, leading to greater life expectancy in this population. With this in mind, it is important that health professionals are providing care that is able to support quality of life and reduce symptoms during this time. Investigating the changes in body composition, physical function, and muscle strength in this population is an important step towards creating guidelines that is able to enrich the remainder of the lives in these patients.

Part 3 of this thesis contains the complete research manuscript addressing the original research question: "Is there a change in body composition, physical function, and muscle strength in patients with metastatic BC between baseline, week 3 and week 6 of chemotherapy?". The design of the study was set up specifically in response to this research question. Unfortunately, due to a low sample size, the research question was not able to be answered with significance. Although power was not reached with the sample size, normal body composition according to gender- specific reference cut-offs, and stable physical function and muscle strength in participants were recorded. While we didn't see a reduction in these three outcomes as hypothesised, findings involving "insufficient" physical activity and poor protein intake amongst majority of the sample size indicate risk of developing sarcopenia/sarcopenic obesity.

Limitations to this study design (addressed in detail in section 3.5) include the restricted five-month recruitment phase, six-week follow up, and having body composition measurements through BIA alone. This research study has future plans of continuation, whereby these limitations will be addressed through continuing recruitment, and following up patient body composition with routine CT scans 6 months post baseline.

With limitations to the study, and preliminary results in mind, recommendations for future research investigating body compositional, physical function, and muscle strength changes in the metastatic BC population during chemotherapy can be made to improve knowledge to influence future intervention studies. Further investigations into this population group may consider exploring barriers and enablers to physical activity, as well as objectively recording physical activity levels through a device over questionnaires to give more accurate results. Investigating participant's knowledge of appropriate nutrition and exercise for their disease will also further our understanding of what resources should be supplied to this population.

Looking forward, further observational studies on nutrition and exercise interventions are required to inform intervention studies in order to provide evidence-based practice guidelines for women with metastatic BC.

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Appendices

Appendix A: Literature Summary Matrix Table

Theme	***Outcomes of sarcopenia/ low fat free mass in patients with cancer***	***Exercise interventions in patients with cancer and/or sarcopenia***	***Nutrition supplementation to improve FFM, physical function, or muscle strength***	***Combined nutrition and exercise interventions to improve FFM, physical function, or muscle strength***
Prado, 2009 [24]	- n=127 prospective study from 2002-2005 - Sarcopenia was a significant predictor of toxicity and TTP regardless of age, performance status and albumin - Toxicity and TTP was significantly higher in sarcopenic patients than non-sarcopenic (62 d vs. 105 d respectively)			
Taffe, 2006 [37]		- Review article on exercise treatment for sarcopenia - 12 weeks of HIT in older men showed an 11.4% increase in muscle cross sectional area of mid-thigh, and >100% increase in muscle strength - RTE is an effective countermeasure for sarcopenia - RTE 1 – 2 times per week is sufficient for improvement in sarcopenia - Aerobic activity has negligible effects on augmenting muscle mass and strength opposed to resistance		
Yoshimura , 2017 [55]		- Systematic review including 7 RCTs (4 exercise) - Very low-quality evidence suggests that exercise interventions may improve muscle mass, muscle strength, and	- Systematic review of 7 RCTs (5 nutrition) - Very low-quality evidence suggests nutritional interventions of EAA, collagen peptide, protein, and	- Systematic review of 7 RCTs (4 combination of nutrition (protein or EAA) and exercise) - Studies included 2 – 3 times a week of comprehensive training

		walking speed after 3 months of intervention - Exercise interventions should contain resistance exercise	tea catechin may be effective in improving muscle strength after 3 months of intervention - HMB, leucine, BCAA, vitamin D and creatine were also potentially beneficial	- Low-quality evidence suggests that combined intervention of exercise and nutrition may have positive effects in improving walking speed after 3 months - No significant effects on FFM, muscle strength or maximum walking speed
Carneiro, 2016 [45]	- 14 studies investigating sarcopenic obesity - Sarcopenic obesity is associated with worse clinical outcomes (mortality) - Prevalence of sarcopenic obesity in cancer: 1 – 29% - Sarcopenic obesity associated with higher risks of DLT (how much higher) and in sarcopenic colorectal cancer with a fivefold higher prevalence of major post-operative complications than non-sarcopenic, although another study found no associations in colorectal cancer - 1 study: 47% of sarcopenic obese participants had worse functional status than non-sarcopenic obese participants - 1 study: sarcopenic obesity, but not sarcopenia or obesity alone was an independent predictor of shorter survival in patients with pancreatic cancer			
Mochamat, 2017 [63]			- Systematic review (n=21) compared treatment with or without vitamin, mineral, protein or dietary supplements in cancer cachexia - Vitamin D: improvement in muscle weakness in prostate cancer	

			- Vitamin C: improvement in several QOL domains in terminal cancer - Vitamin E and Omega-3 FA: showed effects on survival - 1 study: patients gained average of 2kg body weight with HMB, arginine, and glutamine supplementation - 1 study: 470 patients with cancer supplemented with HMB, arginine, and glutamine supplementation found no significant increases to FFM after 8 weeks, but a strong trend in the direction of FFM increase was noted - Carnitine supplementation in patients with advanced pancreatic cancer gained weight with an average of 3% increase in BMI and improved overall survival	
Knols, 2015 [47]		- Systematic review (n=34) RCTs and controlled clinical trials assessed for PE improving PF and psychological well-being in patients with cancer - Patients with cancer in specific populations may benefit from PE during and after treatment - QOL and longevity benefits from PE in patients with cancer may vary with disease stage, treatment & lifestyle - Patients with breast, colorectal, and prostate cancer who are overweight found to have increased cancer recurrence and poorer survival - PE interventions alone are not sufficient		

		to influence weight significantly in overweight patients with cancer during medical treatment - Self-reported QOL improved in the PE intervention groups in most studies reviewed		

Abbreviations:

TTP Time to Tumour Progression

DLT Dose Limiting Toxicity

EAA Essential Amino Acids

BCAA Branched Chain Amino Acids

QOL Quality of Life

RCT Randomised Control Trial

FFM Fat Free Mass

BMI Body Mass Index

HMB Beta-Hydroxy-Beta-Methylbutyrate

PE Physical Exercise

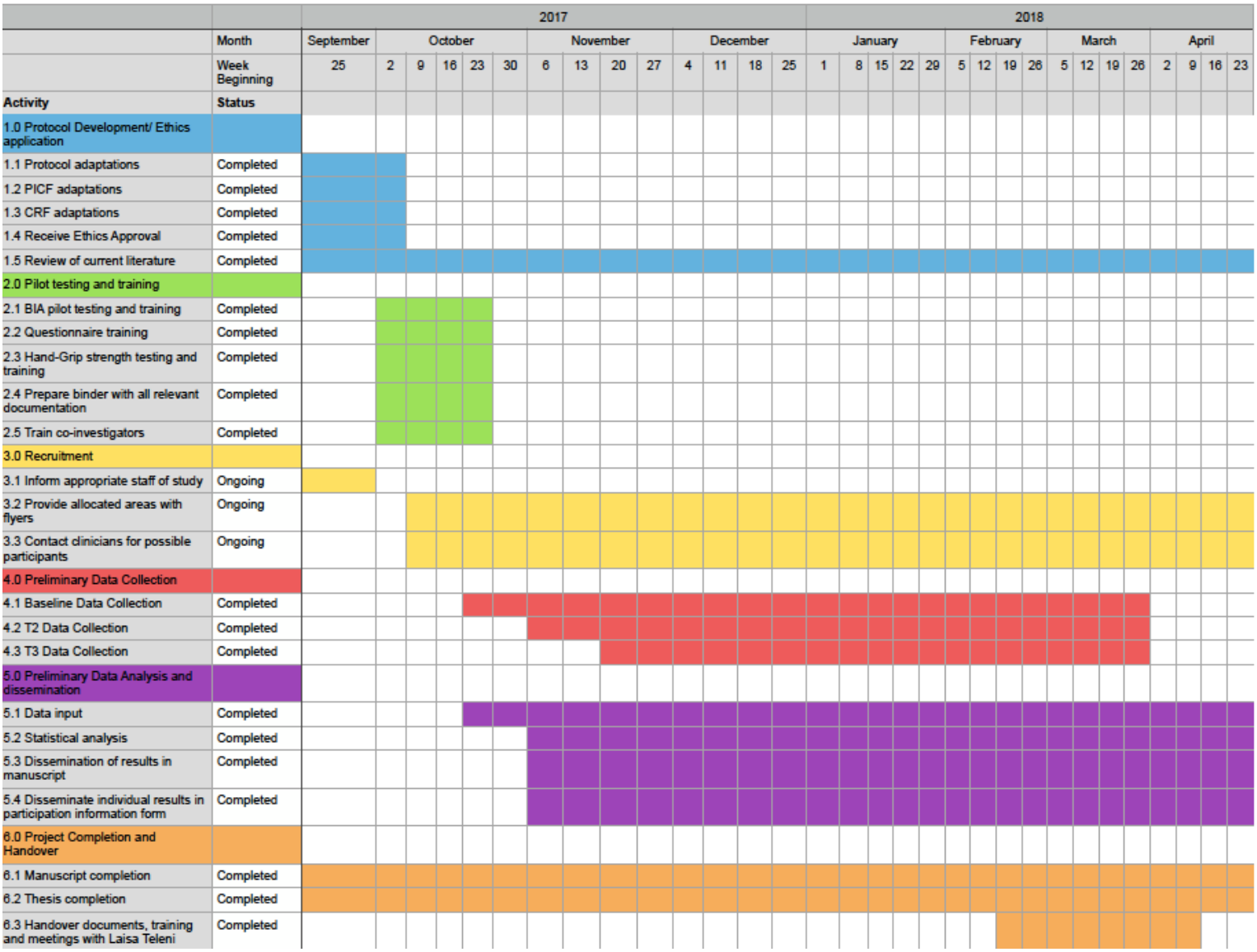
PF Physical Functioning

RTE Resistance Training Exercise

HIT High Intensity Training

FA Fatty Acid

Appendix B: Project Timeline



Appendix C: Ethical Clearance and Approval Letters

The following pages provide the official letter confirming ethical clearance for the BOP study by the Mater Misericordiae Ltd Human Research Ethics Committee.

Mater
Exceptional People. Exceptional Care.

6 October 2017

Dr Barbara van der Meij
L3, Salmon Building
South Brisbane Qld 4101

Dear Dr van der Meij

Re: HREC Ref #: HREC/17/MHS/63
Project title: BODY COMPOSITION AND PHYSICAL FUNCTION DURING CHEMOTHERAPY FOR METASTATIC BREAST CANCER – A PILOT OBSERVATION STUDY

Thank you for submitting the above research project for single ethical review. This project was considered by the Mater Misericordiae Ltd Human Research Ethics Committee (MML HREC) (EC00332) at its meeting held on 18 July 2017 and I further reviewed on 04.09.17, 28.09.17 and 05.10.17.

I am pleased to advise you that the above research project meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007)* and ethical approval for this research project has been granted by the Mater Misericordiae Ltd Human Research Ethics Committee.

The nominated participating site for this project is:

- *Mater Misericordiae Ltd*

Note: If additional sites are engaged prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the MML HREC. Notification of withdrawn sites should also be provided to the MML HREC in a timely fashion.

This letter constitutes ethical approval only. Please liaise with your Research Governance office in regard to any additional requirements. At Mater Misericordiae Ltd please contact the Research Governance Office on 07 3163 3769.

The approved documents include:

Document	Version	Date
Covering Letter		28 June 2017
Application: NEAF Submission Code AU/1/650F215	Version 2.2 (2014)	30 June 2007
Protocol	5	2 October 2017
Participant Information Sheet/Consent Form	5	2 October 2017
Case Report Form	4	2 October 2017

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), updated in 2015. The processes used by this HREC to review multi-centre research proposals have been certified by the National Health and Medical Research Council.

MML HREC Office, Mater Research
Room 294 Level 2 Aubigny Place *Ph: 07 3163 1585 Fax: 07 3163 1588* *Email: research.ethics@mmri.mater.org.au*

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EORTC QLQ-C30	3.0	
Malnutrition Screening Tool: Malnutrition: Is your patient at risk?		
Scored Patient Generated Subjective Global Assessment (PG-SGA)		
Godin Leisure-Time Exercise Questionnaire		
Recruitment flyer	1	18 August 2017
Response to Request for Further Information		Received 29 August 2017
Response to Request for Further Information		28 September 2017
Response to Request for Further Information		3 October 2017
Barbara van der Meij CV *(valid for 2 years)*		
Laisa Teleni CV *(valid for 2 years)*		
Niamh O"Donoghue CV *(valid for 2 years)*		
Amelia Bandera CV *(valid for 2 years)*		
Celia Innerarity CV *(valid for 2 years)*		
CV Natasha Woodward CV *(valid for 2 years)*		

Approval of this project by the MML HREC is valid from **06.10.17** to **06.10.20**, subject to the following conditions being met:

- The Principal Investigator will immediately report anything that might warrant review of ethical approval of the project.
- The Principal Investigator will notify the MML HREC of any event that requires a modification to the protocol or other project documents and submit any required amendments. These instructions can be found at: http://www.materresearch.org.au/about-us/human-research-ethics-and-governance/mater-hrec-application-requirements.
- The Principal Investigator will submit any necessary reports related to the safety of research participants.
- In accordance with *Section 3.3.22(b)* of the National Statement the Principal Investigator will report to the MML HREC annually, the first report is to be submitted by **06.10.18**. Template may be downloaded at: http://www.mater.org.au/Home/Research/Human-Research-Ethics-Committee/HREC-and-RGO-Resources
- The Principal Investigator will notify the MML HREC if the project is discontinued before the expected completion date, with reasons provided.
- The Principal Investigator will notify the MML HREC of any plan to extend the duration of the project past the approval period listed above and will submit any associated required documentation.
- A copy of this ethical approval letter together with completed Site Specific Assessment (SSA) and any other requirements must be submitted by all site Principal Investigators to the Research Governance Office at each participating institution in a timely manner to enable the institution to authorise the commencement of the project at its site/s.

Please confirm your commencement date with the Research Ethics Office.

Should you have any queries about the MML HREC's consideration of your project, please contact the HREC Coordinator on (07) 3163 1585. The MML HREC Terms of Reference, membership and standard forms are available at http://www.materresearch.org.au/about-us/human-research-ethics-and-governance/human-research-ethics.

The MML HREC wishes you every success in your research.

Yours sincerely

Dr Conor Brophy MBBS; MD; MBioethics; FRCP; AFRACMA
Mater Misericordiae Ltd HREC Chairperson
Mater Research

Appendix D1: Developed BIA User Manual

i) BIA user manual: Developed by Amelia Bandera in collaboration with BOP study research team

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Bioelectrical Impedance (BIA)
Impedimed BIS
User manual

Populations not suitable for this measure:

- **Pregnant women**
- **Patients with a pacemaker**

What do you need?

- Impedimed suitcase
- Pen
- Piece of paper
- Scales
- Stadiometer
- Impedimed SFB7 set (stored in second drawer of filing cabinet), charged

Instructions:

- Check the battery status on the display
    - Choose SETUP button to see battery

Step 1: Calibration

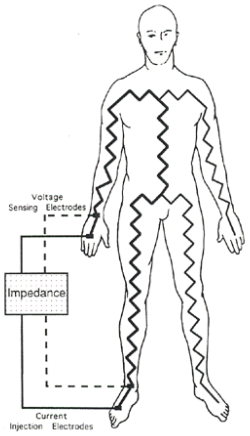
- Calibrate the device before use
    - One a day is sufficient

1. Remove clips from leads and connect the leads to the calibration test cell according to the colour-coding
2. Switch 'on' the machine using the small white button on the front
3. On the main screen, press the "test" button
4. Press the "start" button to make a test reading (you will see a "calculating" screen and after that, a "passed" screen signifies the device and leads are in a good condition)
5. De-attach the leads from the calibration device and re-attach the clips

Step 2: Prepare your patient

1. Measure and record height and weight
2. Record patient's DOB, URN and age

3. Make sure the patient has emptied their bladder before the test
4. Have the patient take off their right shoe and sock (if applicable)
5. Ask patient to remove any jewellery, metal on the body or metal in clothes (e.g. belt, coins in wallet)
6. Position the patient on the bed with the **right** side of the body towards you (use left side in case the subject has an IV in the left arm)



Standard placement of electrodes for whole-body impedance measurements.

7. The legs should be apart, making sure to not touch each other. If needed, place a pillow in between the legs.
8. Instruct the patient to rest for at least 5 minutes
9. Clean the skin of the wrist, hand, ankle and foot with an alcohol wipe
10. Place electrodes on the skin of the wrist, hand, ankle and foot

11. Make sure the electrodes are **5 cm** apart

12. Attach an alligator clip to each of the probe ends of the four leads
13. Use the alligator clips to connect each lead to the tab portion of the electrode

Yello

Red

Blue

Black

14. Apply leads according to the colour code (YELLOW = right wrist; RED = surface of right hand; BLUE = right foot on the ankle; BLACK = dorsal surface of right foot).
15. Press firmly to attach each colour coded lead plug to the similar colour locking socket on the device one by one.
16. Go back to main menu and click on MEASURE
17. Insert URN as file name and click ‘edit’ at the ‘patient details’ box
18. Enter gender, height, age and weight in this screen
19. Press OK

Step 3: Measure

1. Press MEASURE
2. Check electrode placement as suggested on screen
3. Press START
4. Record the results
5. Clean the leads of the device with a detergent wipe. *For patients under contact precautions (the dark green signs) wipe over with the disinfectant wipe twice. Allow it to dry in between.*
6. Use reference values to interpret the results

Typical set-up for measurement.

Appendix D2: Developed JAMAR PLUS User Manual

JAMAR PLUS+ user manual: Developed by Amelia Bandera, and reviewed by Dr Barbara van der Meij

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JAMAR PLUS+
User Manual

What you need:

- JAMAR PLUS+ (Stored in 3rd drawer in filing cabinet)
- Pen
- Paper
- 2 x AAA batteries (if needing recharging); batteries are replaced on the back of the device

Instructions:

1. Check the patient's grip on the JAMAR PLUS+ before commencing: If the patient has smaller-average sized hands, adjust the grip position of the JAMAR PLUS+ to the 2nd lowest rung; if the patient has average-large sized hands, move the grip of the JAMAR PLUS+ to the 3rd lowest rung. To remove the grip position, push the lower end of the handle so that the slotted portion rotates away from the lower shaft. Allow it to then separate from the top shaft. Choose the preferred position and replace the top part of the handle onto the chosen rung, then rotate the lower part of the handle back onto the shaft until it clicks into place.

2. Use the "on/off" button to turn the JAMAR PLUS+ device on.

3. Check that the units of measurement is in kg rather than lbs. This can be seen on the right side of the display. If lbs is highlighted, remove the battery cover on the back of the device. There is a switch under the cover where you can switch lbs to kg.

4. Use the patient's left hand for the test: To select the hand and mode of the test, press the button "select test" until only the "L" is shown in the top left corner on the display.

5. The patient will perform 3 tests for an average score. To choose the number of tests the patient will complete, press the button "# of trials" until the number "3" is highlighted on the top of the display.

6. To begin the test, ask the patient to hold the JAMAR PLUS+ in their left hand while seated. Their left arm should be at a 90 degree angle.

7. Have the patient grasp the JAMAR PLUS+ gently to that the palm fits comfortably to the rear of the instrument

8. Press the "start" key and the number "1" will appear and flash at the top of the display.

9. Give the patient encouragement to squeeze the grip as hard as they can. Record the reading on the display

10. Give the patient 30 seconds recovery and press “test” to repeat for the second, and then third tests.

11. Be sure to record each reading for all 3 tests and transfer measurements to data sheet with patients de-identified number

12. Press the “reset” key to clear the previous settings before moving to the next patient to take measures.

13. When finished using the JAMAR PLUS+, use the “on/off” button to turn off.

Appendix E: Diagnosis of Sarcopenia: Measureable Reference Cut-Off Values [22]

Criterion	Measurement Method	Gender specific cut-off points	Reference group defined	Reference
Low fat-free mass	BIA	≤15.0 kg/m^2	Based on hospital admission patients (*n = 816 females*) compared to gender-, age- and height matched healthy volunteers (*n = 1707*)	[89]
High fat mass	BIA	≥11.8 kg/m^2	Based on hospital admission patients (*n = 816 females*) compared to gender-, age- and height matched healthy volunteers (*n = 1707*)	[89]
Muscle Strength	Hand-grip strength	BMI ≤ 23 ≤ 17 kg BMI 23.1–26 ≤ 17.3 kg BMI 26.1–29 ≤ 18 kg BMI > 29 ≤ 21 kg	Based on quartiles of study group (*n = 5,317*)	[99]
Physical Function	Gait speed (m/s)	Height ≤ 159 cm ≥ 7 s (GS < 0.65 m/s) Height > 159 cm ≥ 6 s (GS < 0.76 m/s)	Based on quartiles of study group (*n = 5,317*)	[99]

Appendix F: Author Guidelines for the Journal of Cachexia, Sarcopenia and Muscle

Journal of Cachexia, Sarcopenia and Muscle (JCSM)

AUTHOR GUIDELINES

AIMS AND SCOPE

The Journal of Cachexia, Sarcopenia and Muscle is a peer-reviewed international journal dedicated to publishing materials that are related to cachexia and sarcopenia, as well as to body composition and its physiological and pathophysiological changes during the lifespan and in response to different illnesses from all fields of the life sciences.

The term cachexia describes involuntary weight loss that is observed in the course of many chronic diseases, and is one of the most debilitating and life-threatening aspects of various illnesses at advanced stages. Cachexia, wasting syndromes and sarcopenia are becoming a concerning challenge for an increasing number of patients, their relatives and the medical teams caring for them. The Journal of Cachexia, Sarcopenia and Muscle aims to offer a reliable resource to all professionals who are interested in related research or who are involved in the clinical care of affected patients, for example those suffering from AIDS, cancer, chronic heart failure, chronic lung disease, liver cirrhosis, chronic kidney failure, rheumatoid arthritis, or sepsis.

Alterations in body composition, particularly those affecting skeletal muscle, are key elements in the ageing process and in the pathophysiology of several chronic illnesses. Sarcopenia, i.e. loss of functional muscle mass without weight loss, is part of the ageing process and may play a role in reduced physical performance, falls, and disability. Studies on the functional importance of fat tissue and mechanisms leading to lipolysis are equally of interest as are studies on mechanisms of muscle wasting.

The pathophysiology of cachexia involves a complex interaction between disease and body. Consequently, numerous potential therapeutic approaches are being considered and developed. Diagnostic and assessment approaches also involve researchers and clinicians seeking better screening and evaluation options and enhanced biomarkers through validated complementary investigations. This makes the Journal of Cachexia, Sarcopenia and Muscle a reliable resource of information for physicians, biochemists, biologists, dieticians, pharmacologists, and students dealing with cachexia, wasting and sarcopenia in various diseases.

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- A concise and informative title. Ideally, the title should include maximum 120 characters or 15 words.
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, telephone and fax numbers of the corresponding author

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Please provide a structured abstract with a maximum of 400 words which should be divided into the following sections:
- Background
- Methods
- Results
- Conclusions

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Please provide 4 to 6 keywords which can be used for indexing purposes.

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Manuscripts should be submitted in Word.

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Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section before the reference list. The names of funding organizations should be written in full.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:
1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

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  Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

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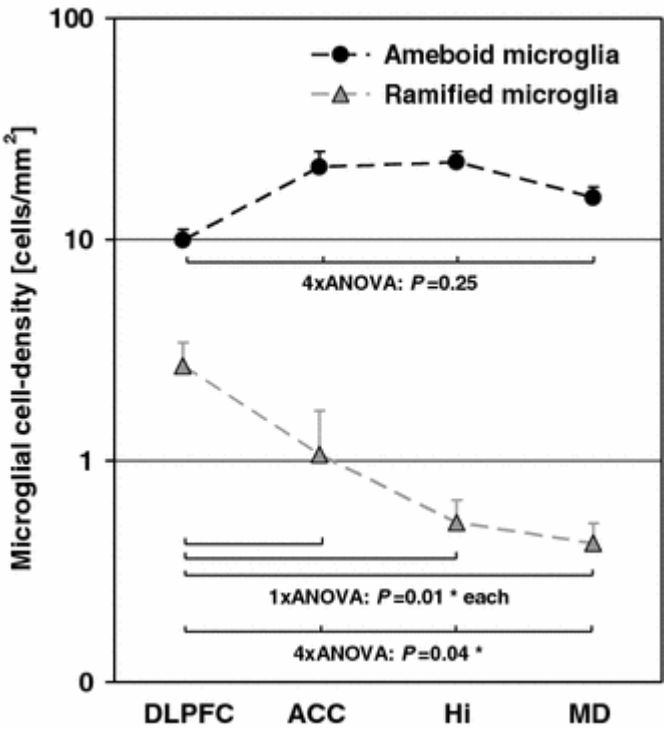

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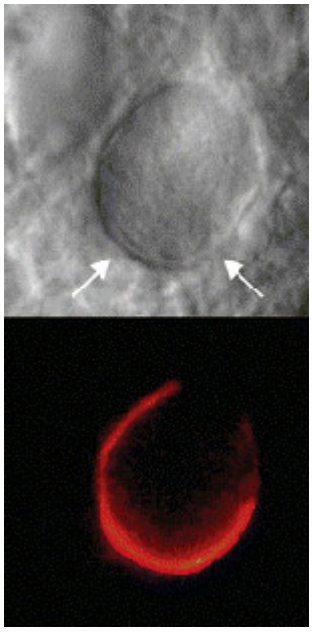

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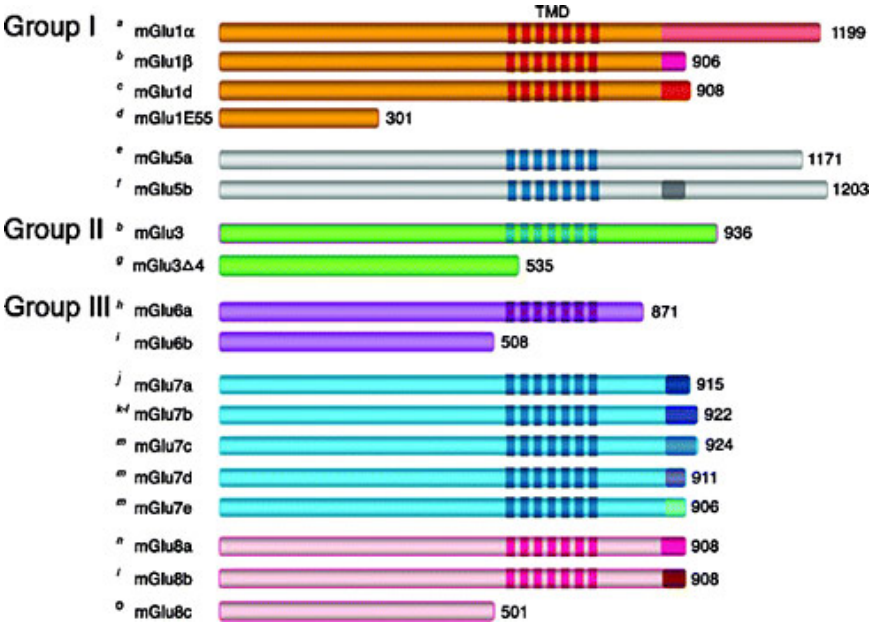

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